REMARKS

Claims 1, 4-14, 17-28, 30-31, 34-44, 47-58, 60-61, 65-73, 86-88 and 90-91 are pending. Claims 2, 3, 15, 16, 29, 32, 33, 45, 46, 59, 62-64, 74-85 and 89 have been cancelled without prejudice. Claims 1, 4, 5-7, 9, 10, 12, 13, 14, 17, 18, 21, 22, 25, 30, 31, 34-44, 47-58, 60-61, 65-67, 69, 70, 72, 73, 90 and 91 have been amended. However, the cancellation and/or amendments to the claims have been made solely to expedite prosecution of the present application. No new matter has been added.

Rejection Under 35 U.S.C.§112, second paragraph

Claims 6, 9, 16-28, 19-23, 36, 39, 46-48, 49-53, 66, 69, 76, 77-83 are rejected under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention."

In particular, the Examiner rejected claims 6, 18, 36, 48, 66 and 78 as being unclear "in the recitation of 'disrupts expression' because it is not clear if the transgene alters the expression levels of transcription or simply disrupts the contiguous sequence of the endogenous gene. The Examiner further rejected claims 6, 18, 36, 48, 66 and 78 because "it is unclear in the recitation of 'or other event' because it is not clear what is encompassed within the metes and bounds of the claim. While transgenic knockout and knockin terminology is defined in the specification and known in the art, other events relating to a transgene which would disrupt the expression of an endogenous gene are not clearly defined."

The claims have been amended, thereby obviating this rejection.

In addition, the Examiner rejected claims 9, 21, 39, 51, 69 and 81 as "unclear in the recitation of 'milk-specific promoter' because it is unclear if the promoter is responsive to milk or that the promoter is active in the mammary gland during lactation as suggested by the group of promoters listed in dependent claims 10, 22, 39, 52, 70 and 82."

Applicants respectfully disagree with this rejection. In view of the description of milk-specific promoters throughout the present application, the meaning of the term is clear. However, to further expedite prosecution of the present application, the claims have been

amended to recite a "promoter preferentially expressed in mammary gland epithelial cells." Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Claims 16, 46 and 76 are rejected as being "unclear and confusing because it recites that the heterologous nucleic acid of the dependent claim should be heterologous."

Claims 16, 46 and 76 have been cancelled, thereby obviating this rejection.

Claims 17, 47 and 77 are rejected as being "unclear in the recitation of 'human sequence' because the metes and bounds of what constitutes a human sequence are not clearly defined. The recited nucleic acid does not have any size or functional limitations. So that a sequence of 5 base pairs from a human gene would most likely find 100% homology with sequences form other species and it would be unclear what would differentiate these sequences."

Claims 17, 47 and 77 have been amend to recite a cell wherein the heterologous nucleic acid sequence encodes a human polypeptide. The amendment to the claims thereby obviates this rejection.

Claims 19-23, 49-53 and 79-83 are rejected as "vague and unclear in the recitation of 'nucleic acid is under the control of a promoter' because a 'nucleic acid' does not necessarily maintain a function that can or would be regulated by a promoter. For example, short nucleic acid sequences of five base pairs would have no function in relation to the promoter"

The claims have been amended such that the nucleic acid sequence encoding a human polypeptide are under the control of a promoter, thereby obviating this rejection.

For the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of Claims 28, 58 and 88 Under 37 CFR 1.75

Claims 28, 58 and 88 are objected to under 37 CFR 1.75 as 'being a substantial duplicate of claim 27, 57, 87." According to the Examiner, "when two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite slight

difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim."

Applicants respectfully traverse this rejection. As provided at page 10, lines 9-11 of the present application, the term "primary derived somatic cells" refers to "primary cells which have undergone at least one subsequent division" than a primary cell. Thus, claims 28, 58 and 88, which are directed to primary derived fibroblasts, claim different subject matter than claims 27, 57 and 87 which are directed to primary fibroblasts. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of Claims 1-5, 7, 12-17, 19, 24-28, 31-35, 37, 42-47, 49, 54-58, 61-65, 67, 72-77, 79, and 84-88 Under 35 U.S.C. §102(b)

Claims 1 and 31 are rejected under 35 U.S.C. §102(b) as "being clearly anticipated by ATCC number CCL-73." In particular, the Examiner states that

> Claims 1 and 31 encompass a purified embryonic or fetal caprine cell. ATCC number CCL-73 is a Capra hircus (goat) primary cell line derived from the esophagus of a male goat embryo at 2/3 term. The cell line has been used and referenced in at least two cited references (1967 and 1994, bottom of specification sheet). Thus claims 1 and 31 are anticipated.

Claims 1 and 31 have been amended to recite a purified embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the cell includes a transgene integrated into its genome. Since ATCC number CCL-73 does not teach or suggest a caprine embryonic cell having a transgene integrated into its genome, this reference does not teach each and every element of the claims. Therefore, ATCC CCL-73 does not anticipate the claimed invention and Applicants respectfully request that the Examiner withdraw this rejection.

Claims 1, 31 and 61 are also rejected under 35 U.S.C. §102(b) as "being anticipated by Amoah et al." In particular, the Examiner states that

> Claims 1 and 31 encompass a purified embryonic or fetal caprine cell. Claim 61 encompasses a method of preparing said cells. Amoah et al. teach the isolation of goat embryos at the morulae and blastocysts stages (page 580; first and second

columns). Use of these methods one can obtain a purified preparation of goat embryonic cells. Thus claims 1, 31 and 61 are anticipated.

Applicants respectfully traverse this rejection. Claims 1 and 31 are directed to a purified embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the cell has a transgene integrated into its genome. Claim 61 is directed to a method of obtaining such an embryonic or fetal somatic cell. At page 10, lines 2-4 of the present application, Applicants define the term "somatic cell" as being "a differentiated cell . . . [t]he cell can be a somatic cell or a cell that is committed to a somatic cell lineage." The term "committed to a somatic cell lineage" is defined as cells isolated on or after day 10 of embryogenesis. See page 10, lines 12-14 of the present application.

Amoah et al. discuss various advances in goat reproduction including in vitro fertilization of caprine oocytes, culturing embryos to the morulae through blastocyst stage in vitro and transfer of such embryos into a recipient. Nowhere in Amoah et al. is purification of an embryonic or fetal somatic cell taught or suggested. Moreover, the morulae and blastocyst stages referred to by the Examiner are earlier in embryonic development than the claimed somatic cells as defined in the present application. Amoah et al. also do not teach or suggest somatic cells obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat. Thus, Amoah et al. do not teach every limitation of the claims and therefore, do not anticipate the claimed invention.

Applicants respectfully request that the Examiner withdraw this rejection.

Claims 1-5, 7, 12-17, 19, 24-28, 31-35, 37, 42-47, 49, 54-58, 61-65, 67, 72-77, 79, and 84-88 are rejected as "being clearly anticipated by Archer et al." According to the Examiner,

> Archer et al. teach two sources of purified goat cells; Ch1Es cells and goat mammary epithelial (GME) cells. Ch1Es cells can be obtained from ATCC (ATCC listing attached) and represent fibroblast cells derived for a goat at 2/3 term. GME cells are primary somatic cells derived from adult early-lactation goats (page 6840; materials and methods). Archer et al. teach a method to derived GME cells. Archer et al. use two retroviral vectors containing heterologous nucleic acid sequences encoding a transgene for hGH and B-galactosidase (page 6841; figure 1). These vectors are used to transduce said goat cells to create goat

cells which contain a transgene and encode a polypeptide (pages 6842-3; Tables 2, 3 and 4 and figure 3). Thus, Archer et al. anticipate the claims.

The claims have been amended to recite a purified embryonic or fetal caprine somatic cell from an embryonic or fetal goat which is derived from a germ cell of a transgenic goat, wherein the cells have a transgene integrated into its genome, and methods of obtaining such cells.

Archer et al. disclose development of retroviral vectors for infusing a vector directly into the mammary gland. Archer et al. disclose testing the efficacy of the viral vectors for infecting various cell lines in order to determine which vector to use for the infusion. However, Archer et al. do not disclose that the viral vector is integrated into the genome of the various cell lines tested. Moreover, the cell lines disclosed by Archer et al. were not obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat. Thus, Archer et al. do not teach or suggest every element of the claimed invention, and therefore, this reference does not anticipate the claimed invention.

Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of Claims 61-91 Under 35 U.S.C. §102(e)

Claims 62-91 are rejected under 35 U.S.C. §102(e) as "being anticipated by Strelchenko et al." According to the Examiner,

> Strelchenko et al. teach a method of establishing a cultured cell (column 44; Example 2). As stated in the first paragraph of the method, the starting cell can be obtained from any type of cell including embryonic and fetal cells (column 44, lines 16-17) and from any animal (column 45; lines 13-15). Examples specific promoters, in particular milk protein promoters (column 12; lines 30-37), specific transgenes encoding specific polypeptides such as hormones, enzymes, plasma proteins and immunoglobulins are recited throughout the specification (for example column 36; lines 7-63). Thus, all of the embodiments of claims 61-91 are anticipated by Strelchenko et al.

Applicants respectfully traverse this rejection. The claims, as amended, are directed to methods of preparing embryonic or fetal caprine somatic cell lines. The method includes obtaining a somatic cell from an embryonic or fetal goat derived from a germ cell of a transgenic

goat, wherein the cell has a heterologous nucleic acid sequence integrated into its genome, and culturing the somatic cell in a suitable medium to obtain a somatic cell line.

Strelchenko et al. disclose totipotent cells useful for cloning animals. Strelchenko et al. disclose that such totipotent cells are different from pluripotent cells. In particular, Strelchenko et al. provide at column 4, lines 27-29 that "pluripotent cells can refer to a cell that cannot give rise to all of the cells in a live born animal." Strelchenko et al. also disclose that the totipotent cells can be converted into transgenic immortalized totipotent cells. See e.g., column 34, lines 32-36 of Strelchenko et al. Since the claimed methods provide somatic cell lines, i.e., a cell line of cells which do not give rise to germ cells, these somatic cells are not totipotent. Therefore, Strelchenko et al. do not teach or suggest somatic cell lines having a heterologous nucleic acid integrated into the genome of such cells. Moreover, Strelchenko et al. do not teach or suggest obtained a somatic cell from an embryonic or fetal goat which is derived from a germ cell of a transgenic goat. Thus, Strelchenko et al. do not teach every element of the claims, and do not anticipate the claimed invention.

Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of Claims 1-91 Under 35 U.S.C. §103(a)

Claims 1-5, 7-17, 19-35, 37-47 and 49-60 are rejected under 35 U.S.C. §103(a) as "being unpatentable over Archer et al. as applied to claims 1-5, 7, 12-17, 19, 24-28, 31-35, 37, 42-47, 49, 54-58 above, and further in view of Amoah et al." In particular, the Examiner states that

> Archer et al. teach isolated embryonic caprine somatic cells which have been transduced with a heterologous nucleic acid encoding a transgene wherein expression of the transgene is under the control of a promoter. Archer et al. teach the transgene hGH, a hormone, and B-galactosidase, an enzyme, and the LTR promoter, however they do not teach milk-specific promoters or all of the specific transgenes recited in the claims. Amoah et al. teach promoters to specifically target expression of a transgene to the mammary gland (page 582, section on Gene Transfer). Further, in the same section, Amoah et al. teach several of the specific transgenes recited in claim 13 which have already been used to produce transgenic goats and teach that other transgenes can also be expressed in the mammary gland. Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to use the methods of Archer et al. to isolate and create caprine cells with promoters and transgenes described by Amoah et al. One having ordinary skill in the art would

have been motivated to use the different transgene constructs described in Amoah et al. in addition or as an alternative to those described by Archer et al. to obtain cell specific expression of transgenes to improve the quality of animal products through genetic improvements or for the production of pharmaceuticals (Amoah page 578; first paragraph). There would have been reasonable expectation of success given the results of Archer et al. in isolated embryonic or GME caprine cells, to obtain an isolated caprine cell with expression of transgenes under the control of milk-specific promoters taught by Amoah et al.

Applicants respectfully traverse this rejection. The claims, as amended, are directed to purified embryonic or fetal caprine somatic cells obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the cell includes a heterologous nucleic acid sequence which is integrated into the genome of the somatic cell, and methods of preparing such cell lines.

Archer et al. discloses testing the efficacy of the viral vectors for infecting various cell lines in order to determine which vector to use for the infusion. However, Archer et al. do not disclose that the viral vector is integrated into the genome of the various cell lines tested. Moreover, Archer et al. does not teach or suggest obtaining the cells from an embryonic or fetal goat derived from a germ cell of a transgenic goat. Instead, Archer et al. focuses on the development of retroviral vectors for infecting mammary gland cells *in vivo*. Specifically, Archer et al. disclose infusions up the teat canal of a goat with retroviral vectors containing human growth hormone driven by the MoMLV long terminal repeat. Archer et al. conclude that "applying gene therapy technology and replication-defective retroviral vectors to directly introduce a foreign gene into a ruminant mammary gland has dramatically reduced the time of production of pharmaceuticals in milk from years to weeks." See page 6844, column 1 of Archer et al.

Amoah et al. discuss various advances in goat reproduction including *in vitro* fertilization of caprine oocytes, culturing embryos to the morulae through blastocyst stage *in vitro* and transferring such embryos into a recipient. Amoah et al. discuss culturing morulae to blastocyst stage embryos *in vitro*. However, embryos in the morula to blastocyst stage are earlier in embryonic development than the claimed somatic cells as defined in the present application. Moreover, Amoah et al. do not teach purification of any goat cells from an embryo or fetus,

generally, or the purification of embryonic or fetal somatic cells, specifically. Amoah et al. also do not teach or suggest somatic cells obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat.

Thus, neither of these references teaches or suggests a purified embryonic or fetal somatic cell obtained from an embryonic or fetal goat derived from the germ cell of a transgenic goat. In addition, neither of these references teaches such cells having a heterologous nucleic acid integrated into its genome.

Applicants also question the motivation to combine these two references to arrive at the claimed invention. Archer et al. focuses on methods of infecting mammary gland cells of live animals in vivo and reports that such methods can be used to infect mammary gland cells in vivo. Amoah et al. disclose culturing embryos at the morula to blastocyst stage and then transferring the embryo into a recipient. The focus of Archer et al. is infecting cells in vivo and Archer et al. do not disclose purifying cells from any stage of an embryo. Thus, how would either of these references motivate one skilled in the art to purify an embryonic or fetal somatic cell which has integrated into its genome a heterologous nucleic acid?

For, the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

The Examiner further rejected claims 1-91 under 35 U.S.C. §103(a) as "being unpatentable over Archer et al. in view of Amoah et al. as applied to claims 1-5, 7-17, 19-35, 37-47, 49-60 above, and further in view of Strelchenko et al. According to the Examiner

> Archer et al. teach isolated embryonic caprine somatic cells which have been transduced with a heterologous nucleic acid encoding a transgene wherein expression of the transgene is under the control of a promoter. Archer et al. teach a transgene which is randomly inserted, however they do not teach a transgene which has been targeted to insert into a specific nuclear DNA sequence. Strenlchenko et al. teach several recombinant DNA techniques known to a person of ordinary skill in the art which includes knockout and introducing base pair mutations into the target nuclear DNA (column 12; lines 38-67). Further, Strenlchenko et al. also teach promoters to specifically target expression of a transgene to the mammary gland (column 12; lines 26-37 and column 15, lines 20-31), and that one can express many types of genes of interest including hormones, enzymes and other pharmaceuticals and recite several of the specific transgenes (column 36; lines 6-67). Therefore, it would have been prima facie

obvious to one having ordinary skill in the art at the time the invention was made to use cells and methods of Archer et al. to isolate and create caprine cells with the promoter and transgenes described in Amoah et al. and Strenlchenko et al., and to target transgene constructs to specific nuclear DNA sequences as taught by Strenlchenko et al. One having ordinary skill in the art would have been motivated to generate caprine cells containing knocko9ut constructs described in Strenlchenko et al. to be used in the creation of transgenic goats through nuclear transfer (Strenlchenko-entire document). There would have been a reasonable expectation of success given the results of Strenlchenko et al. and one of ordinary skill in the art to create caprine cells in which the nuclear DNA has been modified by insertion of a transgene.

Applicants respectfully traverse this rejection. The claims, as amended, are directed to purified embryonic or fetal caprine somatic cells obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the cell includes a heterologous nucleic acid sequence which is integrated into the genome of the somatic cell, and methods of preparing such cell lines.

As discussed above, neither Archer et al. nor Amoah et al, either alone or in combination, teach or suggest the claimed invention. Strelchenko et al. disclose totipotent cells useful for cloning animals. Strelchenko et al. disclose that such totipotent cells are different from pluripotent cells. In particular, Strelchenko et al. provide at column 4, lines 27-29 that "pluripotent cells can refer to a cell that cannot give rise to all of the cells in a live born animal." Strelchenko et al. also disclose that the totipotent cells can be converted into transgenic immortalized totipotent cells. See e.g., column 34, lines 32-36 of Strelchenko et al. Since the claimed methods provide somatic cell lines, i.e., a cell line of cells which do not give rise to germ cells, these somatic cells are not totipotent. Therefore, Strelchenko et al. do not teach or suggest somatic cell lines having a heterologous nucleic acid integrated into the genome of such cells. Moreover, Strelchenko et al. do not teach or suggest obtained a somatic cell from an embryonic or fetal goat which is derived from a germ cell of a transgenic goat. Thus, Strelchenko et al. do not make up for the deficiencies of Archer et al. and Amoah et al. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment. Applicant asks that all claims be allowed. Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 3/20/01

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Version with markings to show changes made

In the claims:

Please cancel claims 2, 3, 15, 16, 29, 32, 33, 45, 46, 59, 62-64, 74-85 and 89.

Please amend claims 1, 4, 5-7, 9, 10, 12, 13, 14, 17, 18, 21, 22, 25, 30, 31, 34-44, 47-58, 60-61, 65-67, 69, 70, 72, 73, 90 and 91 as follows:

-- 1. (Amended) A purified embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat, wherein the cell comprises a transgene integrated into the genome of the somatic cell.

2. (Cancel) The cell of claim 1, wherein the cell comprises a transgene.

3. (Cancel) The cell of claim 2, wherein the transgene is integrated into the genome of the somatic cell.

4. (Amended) The cell of claim [2] 1, wherein the transgene is a heterologous transgene.

5. (Amended) The cell of claim 1, wherein the transgene [includes] comprises a nucleic acid sequence encoding a human [sequence] polypeptide.

6. (Amended) The cell of claim [2] 1, wherein the transgene is a knockout, or a knockin [or other event which disrupts expression of a caprine gene].

7. (Amended) The cell of claim [2] 5, wherein the transgene [is] further comprises a promoter wherein the nucleic acid sequence is under the control of [a] the promoter.

9. (Amended)The cell of claim 8, wherein the tissue-specific promoter is a [milk-specific] promoter preferentially expressed in mammary gland epithelial cells.

10. (Amended) The cell of claim 9, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

12. (Amended) The cell of claim [2] 5, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of a hormone, an immunoglobin, a plasma protein, and an enzyme.

13. (Amended) The cell of claim [2] 5, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

14. (Amended) [The] A purified embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat, [of claim 1,] wherein the cell comprises a heterologous nucleic acid sequence which is integrated into the genome of the somatic cell.

15. (Cancel) The cell of claim 15, wherein the nucleic acid is integrated into the genome of the somatic cell.

16. (Cancel) The cell of claim 14, wherein the nucleic acid is a heterologous nucleic acid.

17. (Amended) The cell of claim [16] 14 wherein the heterologous nucleic acid sequence [includes] encodes a human [sequence] polypeptide.

18. (Amended) The cell of claim 14, wherein the nucleic acid is a knockout, or a knockin [or other event which disrupts the expression of a caprine gene].

21. (Amended) The cell of claim 20, wherein the tissue-specific promoter is a [milk specific] promoter preferentially expressed in mammary gland epithelial cells.

22. (Amended) The cell of claim 21, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

25. (Amended) The cell of claim 14, wherein the [transgene] nucleic acid encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

29. (Cancel) The cell of claim 1, wherein the cell is obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat.

30. (Amended) The cell of claim [29] 1, wherein the germ cell is sperm from a transgenic goat.

31. (Amended) A purified preparation of an embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat, wherein the cell comprises a transgene which is integrated into the genome of the somatic cell.

32. (Cancel) The cell of claim 31, wherein the cell comprises a transgene.

33. (Cancel) The cell of claims 32, wherein the transgene is integrated into the genome of the somatic cell.

34. (Amended) The [cell] preparation of claim [32] 31, wherein the transgene is a heterologous transgene.

35. (Amended) The [cell] preparation of claim 34, wherein the heterologous transgene [includes] comprises a nucleic acid sequence encoding a human [sequence] polypeptide.

36. (Amended) The [cell] preparation of claim [32] 31, wherein the transgene is a knockout, or a knockin [or other event which disrupts the expression of a caprine gene].

37. (Amended) The [cell] preparation of claim [32] 35, wherein the transgene further comprises a promoter wherein the nucleic acid is under the control of [a] the promoter.

38. (Amended) The [cell] preparation of claim 37, wherein the promoter is a tissue specific promoter.

39. (Amended) The [cell] preparation of claim 38, wherein the tissue-specific promoter is a [milk-specific] promoter preferentially expressed in mammary gland epithelial cells.

40. (Amended) The [cell] preparation of claim 39, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

41. (Amended) The [cell] preparation of claim 37, wherein the promoter is a caprine promoter.

42. (Amended) The [cell] preparation of claim [32] 35, wherein the [transgene] nucleic acid encodes a polypeptide selected from the group consisting of a hormone, an immunoglobin, a plasma protein, and an enzyme.

43. (Amended) The [cell] preparation of claim [32] 35, wherein the [transgene] nucleic acid encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

44. (Amended) [The cell of claim 31] A purified preparation of an embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the cell comprises a heterologous nucleic acid integrated into the genome of the somatic cell.

45. (Cancel) The cell of claim 44, wherein the nucleic acid is integrated into the genome of the somatic cell.

46. (Cancel) The cell of claim 44, wherein the nucleic acid is a heterologous nucleic acid.

47. (Amended) The [cell] preparation of claim [46] 44, wherein the heterologous nucleic acid [includes] encodes a human [sequence] polypeptide.

48. (Amended) The [cell] preparation of claim 44, wherein the nucleic acid is a knockout, or a knockin [or other event which disrupts the expression of a caprine gene].

49. (Amended) The [cell] preparation of claim 44, wherein the nucleic acid is under the control of a promoter.

50. (Amended) The [cell] preparation of claim 49, wherein the promoter is a tissue-specific promoter.

51. (Amended) The [cell] preparation of claim 50, wherein the tissue-specific promoter is a [milk-specific] promoter preferentially expressed in mammary gland epithelial cells.

52. (Amended) The [cell] preparation of claim 51, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

53. (Amended) The [cell] preparation of claim 49, wherein the promoter is a caprine promoter.

54. (Amended) The [cell] preparation of claim 44, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of a hormone, an immunoglobin, a plasma protein, and an enzyme.

55. (Amended) The [cell] preparation of claim 44, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin..

56. (Amended) The [cell] preparation of claim 31, wherein the somatic cell is a fibroblast.

57. (Amended) The [cell] preparation of claim 56, wherein the fibroblast is a primary fibroblast.

58. (Amended) The [cell] preparation of claim 56, wherein the fibroblast is a primary derived fibroblast.

59. (Cancel) The cell of claim 31, wherein the cell is obtained from an embryonic goat derived from a germ cell obtained from a transgenic goat.

60. (Amended) The [cell] preparation of claim [59] 31, wherein the germ cell is sperm from a transgenic goat.

61. (Amended) A method of preparing an embryonic or fetal caprine somatic cell line comprising:

(c) obtaining a somatic cell from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the cell comprises a heterologous nucleic acid sequence which is integrated into the genome of the somatic cell; and

(d) culturing the cell in a suitable medium

such that a somatic cell line is obtained.

62. (Cancel) The method of claim 61, wherein the cell line is a genetically engineered cell line.

63. (Cancel) The method of claim 62, wherein the cell comprises a transgene integrated into its genome.

64. (Cancel) The method of claim 63, wherein the transgene is a heterologous transgene.

65. (Amended) The method of claim [64] 61, wherein the heterologous [transgene] nucleic acid sequence encodes [includes] a human [sequence] polypeptide.

66. (Amended) The method of claim [63] 61, wherein the [transgene] sequence is a knockout, or a knockin [or other event which disrupts expression of a caprine gene].

67. (Amended) The method of claim [63] 61, wherein the [transgene] nucleic acid sequence is under the control of a promoter.

69. (Amended) The method of claim 88, wherein the tissue-specific promoter is a [milk-specific] promoter preferentially expressed in mammary gland epithelial cells.

70. (Amended) The method of claim 69, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

72. (Amended) The method of claim [63] 61, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of a hormone, an immunoglobulin, a plasma protein, and an enzyme.

73. (Amended) The method of claim [63] 61, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

74. (Cancel) The method of claim 62, wherein the cell comprises a heterologous nucleic acid.

75. (Cancel) The method of claim 74, wherein the nucleic acid is integrated into the genome of the somatic cell.

76. (Cancel) The method of claim 74, wherein the nucleic acid is a heterologous nucleic acid.

77. (Cancel) The method of claim 76, wherein the heterologous nucleic acid includes a human sequence.

78. (Cancel) The method of claim 74, wherein the nucleic acid is a knockout, knockin or other event which disrupts expression of a caprine gene.

79. (Cancel) The method of claim 74, wherein the nucleic acid is under the control of a promoter.

80. (Cancel) The method of claim 79, wherein the promoter is a tissue-specific promoter.

81. (Cancel) The method of claim 80, wherein the tissue-specific promoter is a milk-specific promoter.

82. (Cancel) The method of claim 81, wherein the milk-specific promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

83. (Cancel) The method of claim 79, wherein the promoter is a caprine promoter.

84. (Cancel) The method of claim 74, wherein the nucleic acid encodes a polypeptide selected from the group consisting of a hormone, an immunoglobulin, a plasma protein, and an enzyme.

85. (Cancel) The method of claim 74, wherein the nucleic acid encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate

decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

89. (Cancel) The method of claim 61, wherein the cell is obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat.

90. (Amended) The method of claim [89] 61, wherein the germ cell is sperm from a transgenic goat.

91. (Amended) A method of preparing a genetically engineered cell line, comprising:

(e) inseminating a female recipient with semen from a transgenic non-human animal;

(f) obtaining a transgenic non-human embryo from the recipient;

(g) obtaining a somatic cell from [a] the embryo; and,

(h) culturing the cell in a suitable medium,

such that a somatic cell line is obtained.